BG

VERIFICATION OF TRANSLATION

RE: PUBLICATION OF UNEXAMINED JAPANESE PATENT APPLICATION NO.Hei-9-263539

I, Kazunori Shibata, Toranomon East Bldg., 7-13, Nishi-Shimbashi 1-chome, Minato-ku, Tokyo, Japan, am the translator of Publication of Unexamined Japanese Patent Application No. Hei-9-263539 and I state that the following is a true translation to the best of my knowledge and belief.

(Signature of Translator) Kazunori Shibata
(Date)This 11th day of October, 2007.

JP-A-9-263539

(54) [Title of the Invention] Therapeutic Agents for Skin Diseases Having an Anti-fungal Action

(57) [Abstract]

[Construction] Therapeutic agents for skin diseases with an itching dermal condition, comprising the cells of lactic acid bacteria as active ingredient.

[Effect] Long-term improving effect is obtained for intractable itching skin diseases in which Candida is deemed to be involved.

[Claims]

[Claim 1] A therapeutic agent for skin diseases comprising a lactic acid bacterium or processed material thereof as an active ingredient.

[Claim 2] A therapeutic agent for skin diseases as claimed in Claim 1, wherein the condition of skin diseases is an itching dermal condition caused by proliferation of an intestinal fungus such as Candida.

[Claim 3] An orally administrable anti-fungal agent comprising a lactic acid bacterium or processed material thereof as an active ingredient.

[Claim 4] An agent as claimed in Claim 1 or 3, wherein the lactic acid bacterium is one of or two or more species belonging

to Lactobacillus, Bifidobacterium, Pediococcus, Streptococcus, Enterococcus, and Leuconostoc.

[Detailed Description of the Invention]

[0001]

[Industrial Applicability of Application]

The present invention relates to a pharmaceutical preparation having a long-lasting improving effect for an itching skin disease caused by proliferation of an intestinal fungus such as Candida.

[0002]

[Prior Art]

Itching skin diseases for which an itching sensation is mainly complained are the most frequently observed diseases in outpatient care of dermatology. Exemplary diseases causing itch include, particularly, eczema, dermatitis, and urticaria, and a variety of pathogenic factors have been known to be involved in allergic conditions and non-allergic conditions in which the causative substance *per se* has an action releasing histamine from mast cells to cause itching. These clinical presentations appear on the epidermis in any form of erythema, papule, bulla, pustule, incrustation, or scale, accompanied by itching. Rupture by scratching of the epidermis in an eczema makes the condition worse, and in some cases no sufficient effect with anti-histaminics and steroids is obtained and in other cases the condition becomes chronic or intractable.

[0003]

In erythema multiforme, nummular eczema, diffusive exanthema, and palmoplantar pustulosis, which are a kind of itching skin diseases which readily become chronic or intractable, there are many unclear problems regarding pathogenesis, though allergy reactions and various infections are considered to be involved. In addition, rupture by scratching of the epidermis or diffusion of a foreign irritant to the whole body through blood flow causes complicated conditions, for example, a complication of nummular eczema and diffusive exanthema, leading to a tendency toward an intractable state. It is presumed that an infection with Candida or production of an anti-Candida antibody is involved in one of pathogenic factors of theses diseases, and thus in some cases administration of an anti-fungal agent results in alleviation or cure.

[0004]

In an atopic dermatitis in infants, there is an intractable case in which a diet therapy using a causative dietary antigen-free diet (food antigen-removal therapy) is almost ineffective for improvement of the state, though it shows a food allergy; in such a state, intestinally excessively proliferated fungi, particularly Candida, are supposed to be involved in many cases. It is considered that the excess proliferation of Candida induces generation of antibodies to

Candida, which usually decrease immunity and readily induce allergic antibodies to foods, inhalants or contactants.

[0005]

It has been reported that among the patients of infant atopic dermatitis which cannot be improved by the food antigen-removal therapy, there are some cases in which the atopic dermatitis is improved by use of an anti-fungal agent when a Candida IgE-RAST shows positive and Candida is detected in stool fungus culture (Michio Matsuda and Makoto Takahashi, Clinical Medicine in Allergy (Allergy no Rinsyo), vol.11 (10) 768-772 (1991). Since then, for the intractable atopic dermatitis which could not be improved by the food antigen-removal therapy, a therapy with an anti-fungal agent has been tried in various locations and achieved some satisfactory results.

[0006]

Oral anti-fungal agents which are currently administered to the patients of intractable skin diseases include amphotericin B (trade name: Fungizone), itraconazole (trade name: Itrizole), fluconazole (trade name: Diflucan), nystatin (trade name: Nystatin), and the like. The drug primarily selected for a man in whom the in vivo proliferation of Candida is limited only in the intestine is Nystatin or Fungizone which is poor in enteral absorption, and for a woman in whom Candida is indigenous in her vagina Itrizole or Diflucan is used.

Currently, the therapy with an anti-fungal agent for various itching skin diseases affords a good result, but the effect is not long-lasting, and it seems that there is a tendency to recur easily within a short period.

[0007]

[Problems to be Solved by the Invention]

At present, Itrizole or Diflucan has been employed as an excellent anti-fungal agent for treatment of intractable skin diseases which are considered to be caused by allergy or infection involving Candida. Since these target eucaryotic fungi, there is a possibility that the organism acquiring the resistance may be generated in some action mechanism. In addition, the use over the long term is accompanied by a risk of adverse reaction such as dysfunction in the kidney or liver. Therefore, a drug which has an action suppressing an allergic reaction efficiently and continuously with no adverse reaction has been needed.

[0008]

[Means for Solving the Problems]

The cells of Enterococcus are known to have a preventive effect against an infection with Candida (Katsuhito Satonaka et al., the 37th Annual Meeting of the Japanese Society for Medical Mycology, pamphlet (1993)). It has also been reported in the Intestinal Flora Symposium and other Meetings that the organisms of lactic acid bacteria, specifically Lactobacillus

and Bifidobacterium, have a pharmacological action involved in a variety of immune functions, but they were not known to show an action like anti-fungal agents and improve the dermal condition.

[0009]

In this situation, the present inventors considered that the proliferation of the intestinal Candida is involved in intractable skin diseases such as palmoplantar pustulosis, nummular eczema, diffusive exanthema, erythema multiforme, and chronic urticaria or atopic dermatitis, and they tried to apply the cells of lactic acid bacteria to the patients suffering from these diseases. As a result, it was found that the dermal condition was improved and the effect was long-lasting. Thus, the present invention was completed.

[0010]

The lactic acid bacterium used in the invention includes any of microorganisms belonging to Lactobacillus, Bifidobacterium, Pediococcus, Streptococcus, Enterococcus, and Leuconostoc. It is also possible to use a mixture of two or more of these organisms. These microorganisms are readily available from the public agency etc. (ATCC, IFO, etc.).

[0011]

The lactic acid bacterium used in the invention includes those used as food or isolated from the feces of healthy persons, and there is no risk of adverse reactions, accordingly. In

applying practically, the bacterium may be used as killed or live cells, or as the processed cells by grinding or extraction with water, and preferably, as thermally processed cells. These may be formulated in a conventional way into tablets or granules with carriers such as starch, lactose, soybean proteins, etc., and excipients such as diluents, binders, disintegrators, lubricants, stabilizer, correctives, etc.

[0012]

Though the amount to be used depends on the condition, age, and the like, the cells as the active ingredient may be administered at 1×10^9 to 5×10^{12} cells a day for an adult in a single or divided doses.

[0013]

[Examples]

Example 1

Enterococcus faecalis NF-1011 (FERM P-12564) (number of cells: 10^6 cells/ml) was inoculated on a Rogosa liquid medium as mentioned below, and cultured at 37°C for 10-16 hours to give a culture broth (number of live cells: about 10^9 cells/ml). The resulting culture broth was centrifuged at 12,000 rpm for 20 minutes to collect the cells, which were then washed twice with distilled water. The resulting cells were suspended in distilled water, and heated at 110°C for 10 minutes to give a suspension of killed cells, which were then dried by hot air drying or lyophilization to give dry killed cells (hereinafter

referred to as a cell sample).

[0014]

The followings show the components of the Rogosa liquid medium.

Trypticase	10 g
Yeast extract	5 g
Tryptose	3 g
Potassium phosphate monobasic	3 g
Potassium phosphate dibasic	3 g
Triammonium citrate	2 g
Tween 80 (surfactant)	1 g
Glucose	20 g
Cystein hydrochloride	0.2 g
Salt solution (see 1 below)	5 ml
Distilled water	1000 ml

(Adjusted to pH 7.0, and sterilized under heating at 121°C for 15 hours)

(1) Salt solution:

$MgSO_4$ $7H_2O$	11.5 g
$FeSO_4$ $7H_2O$	0.68 g
$MnSO_4$ $2H_2O$	2.4 g
Distilled water	100 ml

[0015]

Soybean protein and corn starch were added to the above cells so that the cell number became 10^{11} to 10^{12} cells, and in addition lactose as an excipient was added to prepare granules, which were divided into 2 g-portions and wrapped. The wrapped granules were used to conduct the following examples.

[0016]

Example 2. Clinical Examples

Volunteers were selected from the persons who showed a strong positive response to the immediate-type reaction after 30 minutes or to the delayed-type reaction after 48 hours in the intracutaneous reaction using a Candida culture filtrate (Torii & Co., Ltd.) as an allergen, and for whom a dermatologist determined to be strongly positive in the Candida IgE-RAST. The volunteers were requested to take orally the granules. The results are shown below. There was no report of side effect to be mentioned specially during the term of taking the granules.

[0017]

Clinical Example 1: Man, 29 years old

He was diagnosed as corium-type erythema multiforme. An antibiotic was administered for 2 weeks, but ineffective. The intracutaneous reaction test for allergy was conducted accordingly. The test showed a strong positive response to Candida after 30 minutes and 48 hours, suggesting involvement with infection of Candida or an anti-Candida antibody. Therefore, the agent of the invention was taken orally at a dose of one package/day (about 2×10^{12} cells as the number of cells) for 2 weeks. Thus, he recovered completely from the corium-type erythema multiforme.

[0018]

Clinical Example 2: Woman, 49 years old

She had suffered from chronic urticaria over 5 years,

and an anti-histaminic agent gave no good result. An intracutaneous reaction test for allergy was conducted accordingly. The test showed a strong positive response and an immediate-type allergic reaction to Candida after 30 minutes. Therefore, the agent of the invention was taken orally at a dose of one package/day (about 2×10^{12} cells as the number of cells) for 8 weeks. Thus, she recovered completely from urticaria.

[0019]

Clinical Example 3: Woman, 47 years old

She had suffered from palmoplantar pustulosis over 3 years, and showed a strong positive response to Candida after 48 hours in an intracutaneous reaction test, suggesting involvement of Candida indigenous in the intestine or vagina. Therefore, the agent of the invention was taken orally at a dose of one package/day (about 2×10^{12} cells as the number of cells) for 5 weeks. Thus, the improvement of dermal condition was observed persistently.

[0020]

Clinical Example 4: Woman, 30 years old

She has suffered from nummular eczema and diffusive exanthema over 1 year, and showed a strong positive response to Candida after 48 hours in an intracutaneous reaction test. Further, she had a complication of chronic paronychia due to Candida infection, and so an external preparation of an

anti-fungal agent was applied to the paronychia together with the agent of the invention at a dose of one package/day (about 2×10^{12} cells as the number of cells) for 16 weeks. Thus, the nummular eczema and diffusive exanthema were improved in a middle degree, and she was also making satisfactory progress in chronic paronychia.

[0021]

[Effect of the Invention]

The use of the cells of lactic acid bacteria improves intractable itching skin diseases in which Candida is suspected to be involved, and its effect is long-lasting. In addition, these cells have no adverse effect and do not disturb the effect in the combined use of an external preparation of an anti-fungal agent.

PATENT ABSTRACTS OF JAPAN

(11)Publication number : 09-263539
(43)Date of publication of application : 07.10.1997

(51)Int.Cl. A61K 35/74
A61K 35/74

(21)Application number : 08-103949
(22)Date of filing : 29.03.1996

(71)Applicant : NICHINICHI SEIYAKU KK
(72)Inventor : SUKAI TETSUO
HASEGAWA EIICHI
YAMAMOTO TETSUO

(54) THERAPEUTIC AGENT FOR DERMATOPATHY HAVING ANTIFUNGAL ACTION

(57)Abstract:
PROBLEM TO BE SOLVED: To prepare a therapeutic agent for dermatopathy, comprising a lactic acid bacteria cell and capable of sustainedly suppressing pruritic dermatopathy caused by the proliferation of fungi such as a candida in an alimentary canal.
SOLUTION: This therapeutic agent for dermatopathy comprises one or more of lactic acid bacterial belonging t the genera Lactobacillus, Bifidobacterium, Pediococcus, Streptococcus, Enterococcus and Leuconostoc and th treated substances as active ingredients. Since the lactic acid bacteria are used for foods or a strain separatec from feces of a healthy human, the bacteria have no dangerousness of causing adverse effects. A heat-treated bacterial cell is preferably used. The bacterial cell can suitably be blended with a usually used additive and prepared as a tablet or a granule according to a conventional method. The daily dose of the agent used is 1×10 to 5×1012 cells/adult expressed in terms of the daily amount of the bacterial cell and the active ingredients. Th therapeutic agent is effective against palmoplantar putulosis, eczema nummulare, secondary eruption, erythema multiforme, chronic urticaria, atopic dermatitis, etc.

LEGAL STATUS

[Date of request for examination] 23.05.1997
[Date of sending the examiner's decision of rejection] 27.09.1999
[Kind of final disposal of application other than the examiner's decision of rejection or application converted registration]
[Date of final disposal for application]
[Patent number]
[Date of registration]
[Number of appeal against examiner's decision of rejection]
[Date of requesting appeal against examiner's decision of rejection]
[Date of extinction of right]

(19)日本国特許庁（ＪＰ）　(12)公開特許公報（A）　(11)特許出願公開番号

特開平9－263539

(43)公開日　平成９年(1997)10月７日

(51)Int.Cl.[6]	識別記号	庁内整理番号	ＦＩ	技術表示箇所
Ａ６１Ｋ　35/74	ＡＤＡ		Ａ６１Ｋ　35/74	ＡＤＡＡ
	ＡＤＺ			ＡＤＺＤ

審査請求　有　　請求項の数４　ＦＤ　（全４頁）

(21)出願番号　特願平8－103949

(22)出願日　平成８年(1996)３月29日

(71)出願人　591246849
ニチニチ製薬株式会社
三重県阿山郡大山田村大字宮永239番地の1

(72)発明者　須貝　哲郎
兵庫県西宮市上大市５丁目11－１番－808号

(72)発明者　長谷川　栄一
千葉県佐倉市大崎台４丁目９番地13号

(72)発明者　山本　哲郎
三重県阿山郡阿山町大字延徳院1406番地の69

(54)【発明の名称】　抗真菌作用を有する皮膚疾患治療剤

(57)【要約】
【構成】乳酸菌菌体を有効成分とするそう痒性皮膚症状の皮膚疾患治療剤
【効果】カンジダが関係していると考えられる、難治性のそう痒性皮膚疾患に対して、皮膚症状の長期改善効果がえられる。

【特許請求の範囲】
【請求項１】乳酸菌及びその処理物を有効成分とする皮膚疾患治療剤
【請求項２】皮膚疾患の症状が、腸管内のカンジダ等真菌類の増殖を原因とするそう痒性皮膚症状である請求項１記載の皮膚疾患治療剤
【請求項３】乳酸菌及びその処理物を有効成分とする内服用抗真菌剤
【請求項４】乳酸菌が、ラクトバチルス属、ビフィドバクテリウム属、ペディオコッカス属、ストレプトコッカス属、エンテロコッカス属、ロイコノストック属に属する微生物の１種または、２種以上であることを特徴とする請求項１又は３記載の薬剤
【発明の詳細な説明】
【０００１】
【産業上の利用分野】本発明は、腸管内のカンジダ等真菌類の増殖を原因とする、そう痒性皮膚疾患の持続改善効果を有する製剤に関するものである。
【０００２】
【従来の技術】皮膚科の外来診療において、かゆみを主訴とするそう痒性皮膚疾患は最も多く見られる疾患である。特に湿疹・皮膚炎、蕁麻疹はそう痒を来す疾患のうちの代表的なものであり、病因もアレルギーが性のものや、原因物質自体にマスト細胞からのヒスタミン遊離作用を有しているために発症する非アレルギー性のものなど他種類あることが知られている。これらの臨床像は、そう痒感を伴った、紅斑・丘疹・水疱・膿疱・結痂・鱗屑などのいずれかが表皮に現れる。湿疹反応による掻破行為によって症状が悪化し、抗ヒスタミン剤やステロイド剤が十分な効果を示さない場合や、病因の物質によっては慢性化、難治化する場合もある。
【０００３】慢性化、難治化しやすいそう痒性皮膚疾患の一種である多形紅斑、貨幣状湿疹、撒布疹、掌蹠膿疱症などは、病因について明らかでない部分が多く、アレルギー反応や各種感染症が係わっていると考えられる。また、掻破行為や外来刺激物の血流を通しての全身撒布等が原因で、例えば貨幣状湿疹と撒布疹の併発などの複合症状が生じ、難治化する傾向を示している。これらの疾患の病因の一つにカンジダ感染もしくは抗カンジダ抗体の産生が関与していると推測されており、症例によっては、抗真菌剤内服によって、軽快もしくは治癒するものもある。
【０００４】乳児アトピー性皮膚炎の中で、食物アレルギーを示しながら、原因食餌性抗原を除去した食事療法（食物抗原除去療法）を行っても改善しにくい難治例が存在し、それには、腸管内で過剰増殖した真菌類、特にカンジダが関与しているものが多いと推測されている。カンジダの過剰増殖により、カンジダに対する抗体が産生され、それが通常免疫を低下させ、食物・吸入物・接触物等のアレルギー抗体を誘導しやすくなると考えられている。
【０００５】食物抗原除去療法で改善しない乳児アトピー性皮膚炎患者のうち、カンジダのＩｇＥ－ＲＡＳＴが陽性で、便真菌培養でカンジダが検出される症例に対して、抗真菌剤を使用することによりアトピー性皮膚炎が軽快することが報告されている（松田三千雄、高橋誠：アレルギーの臨床 Vol.11(10)768-772 (1991)）。それ以降、各地で、食物抗原除去療法で改善しない難治性アトピー性皮膚炎に対し、抗真菌剤療法を追試して、一定の効果を上げている。
【０００６】現在、経口の抗真菌剤で難治性皮膚疾患患者に投与されているものとして、アムホテリシンＢ（商品名ファンギゾン）、イトラコナゾール（商品名イトリゾール）、フルコナゾール（商品名ジフルカン）、ナイスタチン（商品名ナイスタチン）などが存在する。第一選択薬として、カンジダの体内増殖が腸管のみに限られている男性に対しては経腸吸収の悪いナイスタチンもしくはファンギゾンを、膣などにカンジダが常在する女性に対してはイトリゾール、ジフルカンを用いている。現在、各種そう痒性皮膚疾患に対する抗真菌剤の治療で、良好な結果が得られているが、効果が持続せず、短期間で再発しやすい傾向が見られているようである。
【０００７】
【発明が解決しようとする課題】現在、カンジダに関係するアレルギーまたは感染症が原因と考えられる難治性皮膚疾患の治療には優れた抗真菌剤として、イトリゾールやジフルカンがあるが、真核生物である真菌を標的とするため、作用機序によっては、耐性を獲得する菌が現れる可能性がある。又、長期使用によっては、腎、肝機能障害などの副作用の危険性がある。そのため、副作用がなく、且つ、アレルギー反応を効率よく持続的に抑える作用を有する薬剤が求められている。
【０００８】
【課題を解決するための手段】エンテロコッカス属に属する菌体には、カンジダ感染に対する防御効果が知られている（里中勝人、他：第３７回日本医真菌学会総会講演要旨集(1993)）。又、乳酸菌、具体的にはラクトバチルス属やビフィドバクテリウム属に属する菌体にも様々な免疫機能に関する薬理作用があることが腸内フローラシンポジウムやその他の学会で発表されているが、抗真菌剤様の作用を示して、且つ皮膚症状を改善することについて知られていなかった。
【０００９】そこで、本発明者らは、腸管内でのカンジダ菌増殖が関与していると考えられる、掌蹠膿疱症、貨幣状湿疹、撒布疹、多形紅斑及び慢性蕁麻疹やアトピー性皮膚炎などの難治性皮膚疾患患者に乳酸菌菌体を投与したところ、皮膚症状が改善され、且つ、その効果が持続することを見いだし本発明を完成させた。
【００１０】この発明に使用する乳酸菌は、ラクトバチルス属、ビフィドバクテリウム属、ペディオコッカス

属、ストレプトコッカス属、エンテロコッカス属、ロイコノストック属に属する微生物であればいずれの菌でも可能である。又、これらの菌体を２種以上混合したものを用いても使用可能である。これらの菌は、公的機関等（ＡＴＣＣ、ＩＦＯ等）から容易に手に入れることが出来るものである。

【００１１】この発明に使用する乳酸菌は、食用に用いられるもの、もしくは健常人の糞便から分離した菌株であるので、副作用の危険性はない。また、実際に投与するには、死菌体又は生菌体、或いは菌体を磨砕、水抽出などの処理をしたものを用いることができるが、好ましいのは、熱処理菌体である。これらを製剤するにはデンプン、乳糖、大豆蛋白等の担体、賦形剤、結合剤、崩壊剤、滑沢剤、安定剤、矯味矯臭剤等の添加物を用いて周知の方法で錠剤や顆粒剤に製剤される。

【００１２】使用量は、症状、年齢等により異なるが、有効成分として１日菌体量として1×10^{9}個～5×10^{12}個を通常成人に対して１日１回又は数回に分けて投与することができる。

【００１３】

【実施例】

実施例１．エンテロコッカス・フェカリス（Enterococcus faecalis）ＮＦ－１０１１（微工研菌寄第１２５６＊４号）を以下に示す組成のロゴサ液体培地に接種し、（菌数：10^{6}個／ｍｌ）、３７℃で１０～１６時間培養し、生菌数約10^{9}個／ｍｌの培養液を得た。得られた培養液を１２，０００ｒｐｍで２０分間遠心分離して集菌し、蒸留水で２回洗浄して菌体を得た。この菌体を蒸留水で懸濁し、１１０℃で１０分間加熱して死菌体懸濁液を作製し、次に、熱風乾燥法あるいは凍結乾燥法など適当な方法で乾燥処理して、乾燥死菌体（以下菌体標品）を得た。

【００１４】ロゴサ液体培地の組成を示す。

トリプチケース	１０ｇ
酵母エキス	５ｇ
トリプトース	３ｇ
リン酸一カリウム	３ｇ
リン酸二カリウム	３ｇ
クエン酸三アンモニウム	２ｇ
ツイーン８０（界面活性剤）	１ｇ
グルコース	２０ｇ
システイン塩酸塩	０．２ｇ
塩類溶液（１のとおり）	５ｍｌ
蒸留水	１０００ｍｌ

（ｐＨ７．０に調整、１２１℃で１５分間加熱滅菌）

（１）塩類溶液：$MgSO_4\cdot7H_2O$　１１．５ｇ
$FeSO_4\cdot7H_2O$　０．６８ｇ
$MnSO_4\cdot2H_2O$　２．４ｇ
蒸留水　１００ｍｌ

【００１５】上記で得た菌体に大豆タンパクとコーンスターチを加え、菌数が10^{11}個～10^{12}個になるように調製し、更に賦形剤として乳糖を加えて顆粒剤を作製し、２ｇづつ分包した。この分包を用いて以下の実施例を行った。

【００１６】実施例２．臨床例

カンジダ培養濾液（鳥居薬品）をアレルゲンとする皮内反応で、３０分後の即時型反応もしくは４８時間後の遅延型反応で強陽性を示し、皮膚科医によってカンジダＩｇＥ－ＲＡＳＴ強陽性と判断された人の中の、ボランティアに飲用してもらった結果を以下に示す。飲用期間中、特筆すべき副作用は報告されなかった。

【００１７】臨床例１　２９歳男性

真皮型多形紅斑と診断され、抗生物質を２週間投与したが無効であった。そのため、アレルギーの皮内反応を行ったところ、カンジダに対して３０分後及び４８時間後に強陽性を示し、カンジダ感染もしくは抗カンジダ抗体が拘わっていることが示唆された。そこで本発明剤を１包／日（菌数にして約2×10^{12}個）を２週間飲用したところ真皮型多形紅斑が完治した。

【００１８】臨床例２　４９歳女性

５年来の慢性蕁麻疹であり、抗ヒスタミン剤等で良好な結果が得られなかった。そのため、アレルギーの皮内反応を調べたところ、カンジダに対して３０分後に強陽性と即時型アレルギー反応を示した。そこで本発明剤を１包／日（菌数にして約2×10^{12}個）を８週間飲用したところ蕁麻疹が完治した。

【００１９】臨床例３　４７歳女性

３年来の掌蹠膿疱症であり、皮内反応でカンジダに対して４８時間後に強陽性を示し、腸内ないし膣内に常在するカンジダの関与が示唆された。そこで本発明剤を１包／日（菌数にして約2×10^{12}個）を５週間飲用したところ皮膚症状の改善状態の持続が見られた。

【００２０】臨床例４　３０歳女性

１年来の貨幣状湿疹および撒布疹を示し、皮内反応でカンジダに対して４８時間後に強陽性を示した。さらにカンジダ感染による慢性爪囲炎を合併したため、抗真菌剤の外用薬を慢性爪囲炎に用い、本発明剤を１包／日（菌数にして約2×10^{12}個）併用して１６週間投与したところ貨幣状湿疹と撒布疹が中等度改善し、慢性爪囲炎も良好な経過を示した。

【００２１】

【発明の効果】乳酸菌菌体を用いることによって、カンジダが関与していると推測できる難治性のそう痒性皮膚疾患が改善され、且つその効果が持続する。又、これらの菌体は、副作用がなく、抗真菌剤の外用剤との併用で

も、その効果を妨げることがない。